Evaluating Effectiveness of Primary Prevention of Cancer
Ed. M. Hakama, V. Beral, J.W. Cullen & D.M. Parkin
Lyon, International Agency for Research on Cancer

CHANGES IN TOBACCO CONSUMPTION AND LUNG CANCER RISK: EVIDENCE FROM STUDIES OF INDIVIDUALS

D.R. Shopland

Division of Cancer Prevention and Control,
National Cancer Institute,
Bethesda, MD, USA

Smoking, especially cigarette smoking, is the single largest cause of cancer mortality in the United States and most of the developed world (US Department of Health, Education and Welfare, 1979). Smoking is an established cause of cancer at several sites, including the lung, larynx, oral cavity, pharynx and oesophagus, and is a contributing factor in the development of cancers of the bladder, kidney and pancreas (IARC, 1986; US Department of Health and Human Services, 1982). More recent data indicate that smoking is a probable cause of cancer of the cervix in women and may contribute to and result in death from stomach cancer in men and women (IARC, 1986). Overall, smoking is responsible for almost one third of all cancer deaths in the United States, most due to cancers of the respiratory system (Doll & Peto, 1981) (in the United States, lung cancer alone now accounts for more than 28% of all cancer deaths annually). This represents more than 150 000 of the approximately 500 000 cancer deaths estimated to have occurred in 1989 by the American Cancer Society (ACS) (American Cancer Society, 1989).

Every medical and public health institution that has conducted an objective review of the scientific evidence has reached the conclusion that cigarette smoking is the single largest cause of excess cancer morbidity and mortality for both men and women. Only the tobacco industry and those affiliated with growing or manufacturing tobacco products seriously question the scientific basis linking smoking and tobacco use to early mortality from cancer and other chronic diseases. Although the evidence linking smoking and cancer is well known and accepted among both the public and scientists, surprisingly little is known about the health benefits from quitting smoking in order to reduce these risks.

Because cigarette smoking contributes such a large burden to overall cancer deaths and rates, it is important from a public health perspective to examine the benefits of giving up smoking. If stopping smoking can reduce an individual's risk of developing the disease, this knowledge could have enormous implications for cancer prevention and control if large numbers of current smokers could be

persuaded to quit. Of particular importance is how much time is required for a current smoker's risk to decline following cessation and whether this risk will approach or equal that of a non-smoker.

The purpose of this paper is to examine what is known about reducing the cancer risks associated with smoking, including a brief examination of data on the possible benefits of smoking low-tar and low-nicotine cigarettes. Sources of information are limited to major prospective and retrospective studies that contain sufficient numbers of ex-smokers to permit conclusions to be drawn. Most of these studies were initiated in the 1950s and early 1960s and included cohorts of individuals born before the turn of the century. During this period, males changed from other forms of tobacco use such as smokeless tobacco, pipes and cigars to cigarettes (Shopland, 1986), and many cohorts of women did not smoke in large numbers or took up smoking in their late twenties or early thirties (Harris, 1983; US Department of Health and Human Services, 1980). Such cohorts would be expected to have lower total lifetime smoking exposures compared with cohorts (particularly women) born after 1900, when cigarette smoking became more socially acceptable (US Department of Health and Human Services, 1980). An exception to this body of evidence is the new ACS Fifty State Study initiated in 1982. This study contains information on 1.2 million men and women who were followed for four years. Results for women are available in more detail than for men; however, data for both men and women will be discussed.

Although this paper will concentrate on the effects of stopping smoking on lung cancer risk, limited data on other cancer sites are included from the new ACS study. Where mortality information is lacking from the most recent follow-up period from these studies, earlier data will be cited.

The prospective cohort mortality studies

In the 1982 Surgeon General's report (US Department of Health and Human Services, 1982), eight major prospective studies were cited that examined the relationship between cigarette smoking and cancer of various sites. At that time, these studies cumulatively represent nearly 20 million person–years of observation and more than 300 000 deaths. At that time also, the ACS Fifty State Study was only in its initial stage of enrolling cases and was thus not available for review. In this paper, data related to the benefit of quitting smoking will be limited to four of the original eight prospective studies, the large case–control study of Lubin *et al.* (1984b), and preliminary data from the new ACS Fifty State Study (Garfinkel & Stellman, 1988). These studies were selected primarily because they contain large numbers of deaths; four of these studies also included women. The reader should refer to the individual references cited for a more complete description of each of the studies.

British Physicians' Study

More than 34 000 men and 6200 women physicians responded to a questionnaire distributed by the British Medical Association in 1951. With few exceptions, all physicians who replied in 1951 were followed to their deaths or for a minimum of 20 years (for males) and 22 years (for females). Data on changes in tobacco-use behaviour were collected at various intervals through 1973. More

than 11 000 deaths from all causes occurred in this population (Doll & Peto, 1976; Doll *et al.*, 1980).

American Cancer Society Twenty-five State Study

During 1959 to 1960, the ACS enrolled slightly more than one million men and women in their Cancer Prevention Study I (ACS Twenty-five State Study). This cohort was followed for a total of 12 years; nearly 93% of all survivors were successfully traced. Although not a representative sample of the US population, all segments of the population were included except groups that were difficult to trace. More than 150 000 deaths were recorded, including more than 2500 lung cancer deaths (Hammond, 1966; Hammond *et al.*, 1977).

US Veterans' Study

This study followed the mortality experience of nearly 300 000 veterans who held Government life insurance policies in the 1950s. Almost all policy-holders were white males. More than 107 000 deaths occurred in this population during the first 16 years of follow-up. Twenty-six-year follow-up information has been collected, but not reported, on this cohort. Data in this paper will be limited to information published for the first 16 years. More than 3000 lung cancer deaths were recorded among this cohort (Kahn, 1966; Rogot & Murray, 1980).

Japanese study of 29 health districts

In 1965 265 000 Japanese men and women were enrolled in a prospective study in 29 health districts, representing between 90 and 99% of the total population 40 years and older. Follow-up information reported from this study has been sporadic. Data for women have been limited primarily to the first five to eight years of follow-up. Data for men have been reported through 13 years. More than 40 000 total deaths have occurred among the cohort, including more than 10 000 cancer deaths (Hirayama, 1974, 1977).

American Cancer Society Fifty State Study

In September 1982, the ACS initiated Cancer Prevention Study II in which 1.2 million men and women in all 50 states were enrolled in a prospective design. Initial results of this study are just now emerging. Currently, there is more complete information on women than men. By July 1988, death certificates had not been received for about 9% of male and 13% of female deaths. A total of 1006 lung cancer deaths among the cohort of 619 225 women were recorded (Garfinkel & Stellman, 1988).

Differences in lung cancer risk and smoking behaviour between men and women

Epidemiological research over 30 years has conclusively demonstrated that cigarette smoking is associated with a significantly elevated risk of developing and dying from lung cancer. Two major reviews examining this relationship have been published: *The Health Consequences of Smoking: Cancer. A Report of the Surgeon General* (US Department of Health and Human Services, 1982) and the 1986 *IARC Monograph on Evaluation of the Carcinogenic Risk of Chemicals to Humans: Tobacco Smoking* (IARC, 1986).

For men, the average lung cancer risk was about 10 to 12 times greater if they smoke than for men who have never smoked. Among women cigarette smokers, the lung cancer risk was also elevated, but the ratio between smokers and non-smokers was not as high as that for males. The differences between male and female smokers and non-smokers primarily reflected the observed historical differences in total lifetime smoking experiences between the sexes. Men began cigarette smoking earlier than women, they smoked more cigarettes per day, inhaled more deeply, had smoked for longer periods of time, and consumed cigarettes with a tar content higher than those smoked by women.

In the United States, more than half of all men were classified as regular smokers according to studies and surveys conducted over the previous 60 years. In fact, a majority of males were probably regular cigarette users by the end of the first world war or soon after (US Department of Health and Human Services, 1980). In comparison, only 18% of adult women were smokers in 1935 (Fortune Magazine, 1935). Even as late as 1955, twice as many men as women smoked (Haenszel *et al.*, 1956); in the ten-year period between 1955 and 1965, male smoking remained stable at more than 50%. Female smoking rates during this period increased to around 34% – the highest smoking prevalence rate ever reported for adult females in the USA (US Department of Health and Human Services, 1980). Today, women smoke fewer cigarettes per day than men, and more men than women are heavy smokers (National Center for Health Statistics, 1986). When smoking behaviour is examined by individual birth cohorts, further differences between men and women are apparent. Some male cohorts have cigarette-use rates exceeding 70%, whereas no cohort of women is observed to have smoking rates higher than approximately 50% (Harris, 1983; Shopland, 1987). Furthermore, most women currently at risk for developing lung cancer did not begin smoking until well into their twenties or early thirties, whereas the vast majority of men began regular smoking during adolescence (McGinnis *et al.*, 1987). Males also have a history of substantial use of pipes and cigars whereas few females ever smoked these products (US Department of Health and Human Services, 1980).

Cigarette dose and lung cancer risk

The risk of developing and dying from lung cancer is strongly dependent on the total lifetime dose of cigarette smoke. In the prospective studies, lung cancer mortality has been examined by number of cigarettes smoked per day, length of time one has smoked, age of initiation, inhalation characteristics, and tar and nicotine content of cigarettes used. Table 1 provides data for lung cancer risk overall by number of cigarettes smoked daily for males and females. Generally, the higher the daily consumption of cigarettes, the greater the risk. Lung cancer mortality ratios among heavy smoking males are 20 or more times higher than in non-smoking males. For females, the risks also increase with increasing numbers of cigarettes smoked; but even for women who smoke heavily (i.e., two or more packets daily), the risk for lung cancer is lower than that among men who smoke similar numbers of cigarettes.

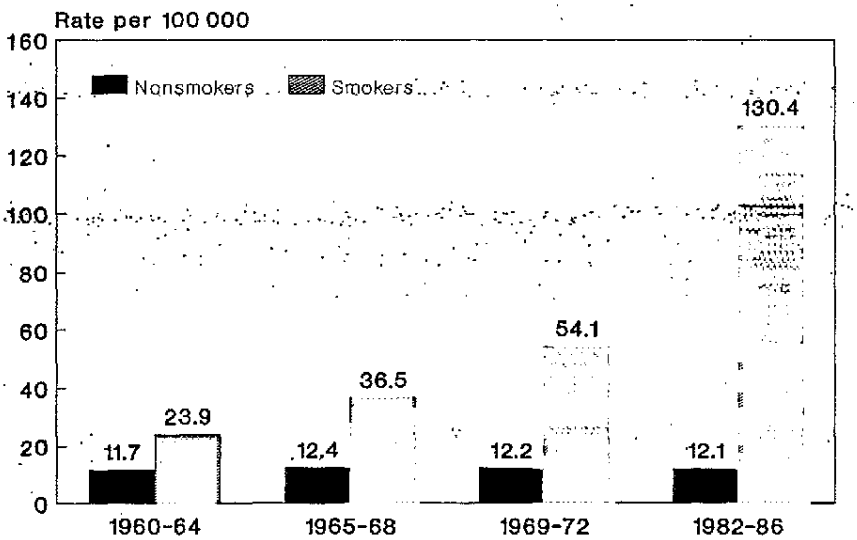
Table 1. Lung cancer mortality ratios for men and women, by current number of cigarettes smoked per day – prospective studies

Population	Men		Women	
	Cigarettes smoked per day	Mortality ratios	Cigarettes smoked per day	Mortality ratios
ACS 25 State study	Non-smoker	1.00	Non-smoker	1.00
	All smokers	8.53	All smokers	3.58
	1–9	4.62	1–9	1.30
	10–19	8.62	10–19	2.40
	20–39	14.69	20–39	4.90
	40+	18.71	40+	7.50
British Doctors' study	Non-smoker	1.00	Non-smoker	1.00
	All smokers	14.00	All smokers	5.00
	1–14	7.80	1–14	1.28
	15–24	12.70	15–24	6.41
	25+	25.10	25+	29.71
US Veterans' study	Non-smoker	1.00		
	All smokers	11.28		
	1–9	3.89		
	10–20	9.63		
	21–39	16.70		
	> 40	23.70		
Japanese study	Non-smoker	1.00	Non-smoker	1.00
	All smokers	3.76	All smokers	2.03
	1–19	3.49	< 20	1.90
	20–29	5.69	20–29	4.20
	40+	6.45		
ACS 50 State study	Non-smoker	1.00	Non-smoker	1.00
	All smokers	22.36	All smokers	10.80
			1–10	5.50
			11–19	11.20
			20	14.20
			21–30	20.40
			31+	22.00

Data from the new ACS Fifty State Study, however, show that the lung cancer risk among smokers has increased in more contemporary cohorts of both men and women (Table 2). Among current smokers, the lung cancer risk ratio has doubled among male smokers compared with results in the earlier ACS prospective study, increasing from approximately 11 to 22. The lung cancer risk for women has increased approximately four-fold from 3 to 12. This risk is almost identical to that observed among men in earlier studies initiated in the 1950s. Such changes indicate that among continuing smokers, the lung cancer risk has increased in more contemporary cohorts having a higher lifetime cigarette experience compared with cohorts enrolled in earlier studies. Ratios for most other cancer sites related to smoking have also increased in the period between studies, particularly for cancers of the respiratory system. The age-standardized lung cancer rate in non-smoking women, however, remained unchanged in the 26-year period covered by the two ACS studies (Figure 1). A similar pattern for

men was reported in the 1989 Surgeon General's report (US Department of Health and Human Services, 1989).

Figure 1. Lung cancer death rates among smoking and non-smoking women over time adjusted to the 1970 US population



Source: Garfinkel and Stellmann (1988)

Cessation of smoking and reduced cancer risks

Data from the cohort mortality studies offer some insight into the benefits of stopping smoking compared with the risk of continuing to smoke. More recent data from the ACS Fifty State Study and the large case-control investigation of Lubin *et al.* (1984a) offer substantial insight into these risks among more recent groups of smokers and former smokers compared with studies initiated in the 1950s and 1960s.

Table 2 presents cancer mortality ratios from ACS Twenty-five State Study (initiated in 1959) and Fifty State Study (initiated in 1982) for both male and female current and former smokers. Data from the Twenty-five State Study is taken from the first six-year follow-up period rather than the 12-year period to make a more direct comparison with findings in the Fifty State Study. Current smokers from both studies are defined as 'cigarettes only' smokers. Ratios represent overall differences between continuing smokers and former smokers regardless of other factors such as length of time since last cigarette, number of cigarettes smoked per day, and duration of smoking.

Among males, the lung cancer risk for former smokers is less than half of that for current smokers. A similar finding is observed among women. For each cancer site, former smokers experience lower mortality compared with those classified as current smokers.

Table 2. Mortality ratios for males and females 35 years and older according to smoking status at time of enrolment

Cancer site	25-State study		50-State study	
	Current smoker	Former smoker	Current smoker	Former smoker
Males				
Lung	11.35	4.96	22.36	9.36
Oral	6.33	2.73	27.48	8.80
Oesophagus	3.62	1.28	7.60	5.83
Larynx	10.00	8.60	10.48	5.24
Bladder	2.90	1.75	2.86	1.90
Pancreas	2.34	1.30	2.14	1.12
Kidney	1.84	1.79	2.95	1.95
Females				
Lung	2.69	2.59[a]	11.94	4.96
Oral	1.96	1.89[a]	5.59	2.88
Oesophagus	1.94	2.15[a]	10.25	3.16
Larynx	3.81	3.10[a]	17.78	11.88
Bladder	2.87	2.31[a]	2.58	1.85
Pancreas	1.39	1.38[a]	2.33	1.78
Kidney	1.43	1.47[a]	1.41	1.16
Cervix	1.10	1.32	2.14	1.94

[a] Ratio is for current and former smokers combined.
Source: US Department of Health and Human Services (1989)

Time since smoking stopped and lung cancer

Data published over the past several decades have consistently shown that the longer one smokes cigarettes, the greater the lung cancer risk. Thus, any benefit from stopping smoking relating to reducing one's lung cancer risk is dependent to a large degree on the total duration of the behaviour before quitting. A number of prospective and case–control studies have examined this issue.

In all four earlier prospective studies (Table 3), lung cancer mortality risk was much lower among former male smokers than among continuing smokers, and this risk was strongly correlated with the length of time ex-smokers remained off cigarettes. In the US Veterans' (Rogot & Murray, 1980) and British Physicians' (Doll & Peto, 1976) studies, those former male smokers who had quit smoking and were able to stay off cigarettes for 15 years experienced lung cancer mortality risks between a half and a sixth of those observed in continuing smokers. However, even among former smokers who had quit for 15 or more years, lung cancer risk was two to four times higher than for lifelong non-smokers. Data from the Japanese study point in the same direction (Hirayama, 1974).

Thus, although giving up smoking appears to reduce one's risk of developing lung cancer, some elevation in risk may remain among former smokers for many years after quitting.

Table 3. Lung cancer mortality ratios in ex-cigarette smokers, by number of years stopped smoking

Study	Years stopped smoking	Mortality ratio	
British doctors	1–4	16.0	
	5–9	5.9	
	10–14	5.3	
	15+	2.0	
	Current smokers	14.0	
US veterans[a]	1–4	18.83	
	5–9	7.73	
	10–14	4.71	
	15–19	4.81	
	20+	2.10	
	Current smokers	11.28	
Japanese males	1–4	4.65	
	5–9	2.50	
	10+	1.35	
	Current smokers	3.76	
		Number of cigarettes smoked per day	
		1–19	20+
ACS 25 State (males 50–69)	< 1	7.20	29.13
	1–4	4.60	12.00
	5–9	1.00	7.20
	10+	0.40	1.06
	Current smokers	6.47	13.67

[a] Includes data only for ex-cigarette smokers who stopped for other than doctors' orders
Source: US Department of Health and Human Services (1982)

A consistent finding in the major prospective studies is that recent former smokers (those who had stopped smoking for less than five years) experienced much higher lung cancer mortality rates than other groups, including smokers who continued to smoke. In the US Veterans' study, for example, former smokers who had been off cigarettes for four years or less experienced a lung cancer mortality ratio of 18.8 compared with 11.3 for current smokers. A similar pattern is observed in other studies. This finding probably reflects that a certain proportion of smokers stopped smoking because they were diagnosed with lung cancer or exhibited symptoms of ill-health. With each additional time interval off cigarettes, however, the lung cancer mortality ratio between former smokers and never-smokers grows smaller. No data regarding lung cancer risk among former female smokers are available from these early studies.

A large case–control study by Lubin *et al.*, involved 7181 male and female lung cancer patients from five Western European countries admitted to hospitals between 1976 and 1980 (Lubin *et al.* 1984a). For each patient, two controls were selected and matched on a number of variables, including age at diagnosis,

sex, centre, and category of hospital accommodation. Controls represented patients in whom diseases not related to tobacco use had been diagnosed. Patients were categorized according to smoking status and duration of smoking behaviour. For individuals who had stopped smoking, the length of time they had been off cigarettes was recorded. As smoking duration increased, the risk of developing lung cancer increased among those individuals who continued to smoke. Among ex-smokers, however, the risk declined for both men and women with the number of years off cigarettes, although among men the rate of decline was greater for those males who had smoked for a shorter length of time (Table 4). After ten years of not smoking, individuals who had smoked 19 years or less experienced a lung cancer risk similar to those who had never smoked. Risks remained elevated among both men and women who were classified as smoking for 20 years or more regardless of the time reported off cigarettes. Among men who had smoked the longest (greater than 50 years), even after stopping smoking for more than ten years, the lung cancer risk was not appreciably different from that of continuing smokers.

Table 4. Relative risk of developing lung cancer by time since stopping smoking and total duration of smoking habit

Time since stopping smoking (years)	Duration of smoking habit (years)			
	1–19	20–39	40–49	> 50
Men				
0	1.0[a]	2.2	2.8	3.0
1–4	1.1	2.1	3.3	3.8
5–9	0.4	1.5	2.2	2.8
> 10	0.3	1.0	1.6	2.7
Women				
0	1.0[b]	2.1	2.7	5.2
1–4	1.0	2.3	2.1	7.1
5–9	0.4	2.0	1.1	1.7
> 10	0.4	0.8	2.3	

[a] Baseline category. Risk for people who had never smoked relative to that for current smokers who had smoked for one to 19 years was 0.3.
[b] Baseline category. Risk for people who had never smoked relative to that for current smokers who had smoked for one to 19 years was 0.6.
Source: Lubin *et al.* (1984a)

These investigators also examined the impact of quitting smoking on lung cancer mortality by type of cigarette smoked, frequency and depth of inhalation, number of cigarettes smoked daily, and number of years off cigarettes (Table 5). The authors concluded: 'The results show that changes in patterns of cigarette smoking that lower exposure were associated with lower risks of developing lung cancer but, when compared with completely stopping smoking, the reductions in risk were small'.